

Role of Placebos versus Antidepressants and Contribution to the Doctor-patient Relationship

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Current literature provides arguments against and in favor of the discussion on effectiveness of the antidepressant medication. Both the methodology, study models and tools used for comparing effectiveness of medications cause controversy. This debate becomes harder when considering the existence of placebo effects in results that promote or question the use of these drugs. Understanding placebo actions not only allows us to better understand the research results regarding use of antidepressants, but additionally, regarding effectiveness of the various treatments that today are used in mental health.

Key Words: placebo effect, antidepressant agents, mental health.

EFFECTIVENESS OF ANTIDEPRESSANTS

The debate regarding antidepressants effectiveness has been an issue since the moment they started to be used massively. Various opinions, both in favor and against it have arisen in time, but when comparing its effect with studies involving placebos, some doubts regarding its usefulness when performing studies aimed to extrapolate results to clinical internship. If we understand that a placebo is a substance with no active potential, we should wonder then why, in randomized studies on antidepressants effectiveness, it seems that placebos have a therapeutical potential that is -many times- similar to that of drugs, or at least it does not allow to prove that active substances are more clinically effective.

Moncrieff's⁽¹⁾ Action Model focused on drugs highlights that psychiatric drugs may be considered as psychoactive substances, if we think they pass into the blood-brain barrier

thus affecting brain functioning, and causing some specific mental/physical disturbances in any person who uses them. These people may consider this condition is more desirable than the original mental disturbances. According to the foregoing, the role that these drugs should have is not related to treating a mental disturbance from its origin, thus causing long lasting results, but rather leading to bearable mental conditions which allow the patients to have a regular daily life.

One of the reasons why patients use antidepressants is because of the potential adjustment of base neurochemical imbalance which could be root of the pathology and, therefore, lead to that so longed "normality"⁽¹⁾. However, a review made by Khan et al.⁽²⁾ reported that a higher effectiveness of antidepressants is achieved against placebos in less than half of the studies made. On the other hand, there is no clear correlation between the medication and specific disease as a treatment⁽¹⁾. In clinical tests made in 1982, antidepressants were --as an

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average-- 6 points more effective than placebos when compared by using the Hamilton's Scale. This difference decreased 3 points --as an average--, in 2008⁽³⁾, which leads to questioning what changes happened during the last few decades so that the effect of antidepressant medication has such a huge variation.

An analysis of randomized tests --made on antidepressants effects in the short term-- in placebo-controlled⁽⁴⁾ major unipolar depression, shows the rate of responders to antidepressants and a placebo is 50% and 30% respectively. The traditional calculation of the antidepressant-placebo difference (50-30=20%) in these pharmacological tests is based on the assumption that placebo responders should be antidepressants responders. Such assertion has never been neither investigated nor proved, given the complexity involving the methodology of the studies aimed to prove such theory.

When making a review of the literature, it is very easy to find studies with contradictory results. The sampling size seems to be the hardest difficulty. In 2004A a review was made by Moncrieff et al.⁽⁵⁾ including 9 studies, with a total of 751 participants, after clearing the variables which could cause a bias on results, concluded that antidepressants and placebos effects do not have a statistically significant difference. On the other hand, updated reviews, just as that made by Cipriani et al.⁽⁶⁾ in 2018, comparing effectiveness of 21 antidepressants versus placebo, where 522 studies were included with a total of 116,477 participants, concluded that all antidepressants proved a significant reduction of depressive symptomatology in adults suffering depression. However, results reported by studies made on pathologies, such as depression seem to be influenced more than just the time when they were made or its methodology, as even studies with similar characteristics made in the same years report significant differences in their results, thus leading to questioning if other factors, such as duration time of the studies could have a relevant significance on results. Just as stated by Hegerl and Mergl⁽⁷⁾, duration of effectiveness studies has changed in time, from an average of 4 to 6 week, therefore, including patients who suffer acute depression conditions, even one of 12 weeks in the studies made during the last two decades, which could

impact on clinical tests results, as the natural course of the disease becomes a distractor.

Beneficial effects of ISRS are not yet determined whether if they are superior to adverse effects⁽¹⁾, although some reviews have been made, such as that of Arroll et al.⁽⁸⁾ who regarding depression determined for the ISRS a number necessary to (NNT) from 7-8, and a number necessary to damage, from 20-90. On the other hand, a review made by Bighelli et al.⁽⁹⁾, of 41 studies, with 8,252 participants, compared antidepressants effects versus placebo for managing panic disorder in adults, reports a slight bias in terms of its higher beneficial effect in antidepressants, but it highlights that NNT was 7. Therefore, it calls our attention that NNT has not had a variation in time, but despite of all this, when analyzing various effectiveness studies against the placebo during the last few years, we still have mismatching results.

Regarding antidepressants effectiveness in severe pathologies, Leuchter et al.⁽¹⁰⁾ studied cerebral functions of people with a diagnosis of major depression treated with antidepressants or placebo. They observed that both groups obtained similar results by reducing depressive symptoms, with the beginning of the study, however, the two groups did not have any physiological equivalence, even though both affected functions of the prefrontal brain region, their mechanism was contrariwise. The study reported that people responding to placebo had a significant increase of their functions, while those using antidepressants reported a reduction in the functions in such area. This proved that placebos and antidepressants could have various action mechanisms; therefore, the response to each of them could be completely independent among them, and there are no overlapping results; thus generating a bigger problem when trying to interpret results and evaluate the methodology carried out for clinical tests.

Unlike the effect of antidepressants in young adults, whose actual result is well known and widely studied, elderly people have more comorbidities, as well as social determinants having a higher risk of suffering psychiatric pathologies, such as depression⁽¹¹⁾. For them it is quite important to consider the type of therapies to be used and their effectiveness. The systematic review made by Wilson et al.⁽¹²⁾, aimed to

analyze the effect of antidepressant medication in elderly patients, reported higher effectiveness to reduce depressive symptoms by using drugs, compared with placebos, apart from a similar response to these drugs when comparing with younger adults. Along with this, a more updated review of the literature reported that even though the ISRS were not better than placebos, when reaching disease remission at 8 weeks, did report to have higher effectiveness to prevent recurrence⁽¹³⁾. Even though there is favorable literature aimed to avoid relapse risk in these patients, that is still not enough. Long term effects of these drugs – both for adults and for elderly people is still under question.

Considering that NNT of drugs antidepressants has not has any significant changes during the last 10 years, and according to Moncrieff statements that there is no direct correlation between psychiatric medication and specific diseases⁽¹⁾, it is necessary to evaluate, in the public health area, if the benefit of these drugs is enough to consider its use in primary care as unique therapy, chosen before other therapeutical, such as psychotherapy or complementary therapies (acupuncture, physical exercise, among others). When focusing only on if antidepressant effect is higher than the placebo effect, there are many doubts whose grounds are questioning the use of placebos, and the difficulty to correlate this to the current clinical reality⁽⁷⁾.

Findings made by Li et al.⁽¹⁴⁾ provide an interesting perspective stating that more severe patients are more willing to remain in studies with placebos, while -on the other hand- Hegerl and Mergl state that the fact of not knowing what they are consuming, along with the participation of patients coming from countries having a poor health coverage –where there is a belief that if they participate in clinical tests that could mean to potentially receive that so longed active component. This situation would make that participants adulterate the information provided in the Hamilton's Scale, in order to look like having a more severe range of symptoms; therefore, this could imply they would be included in the studies; and on the other hand this would influence the patient's attitude to receive the pills⁽⁷⁾.

PLACEBO RELEVANCE

If there is a great deal of research casting doubts on the effectiveness of antidepressant medication, then why do these work? McCormack and Korownyk⁽¹⁵⁾ made a paper commenting about Cipriani et al's review.⁽⁶⁾ They stated that in the placebo groups the average improvement response ranges between 30 to 40%. They interpret that an Odds Ratio of 1.6 means 10-12% of higher improvement in the treatment group against the placebo group. In other words, if 10 patients with suffering moderate and severe depression take antidepressants during 8 weeks, five of them (50%: 40% per placebo plus benefit of 10%) would report to feel better, but in four of them this improvement is not due to the drugs. ¿What allowed that those 4 people felt better with the placebo?

In other words, this effect occurs in a medical setting. a physician gives a patient a pill, but the patient does not know that pill is made of sugar only. This is the placebo. The patient's health further feels better, as the patient believed the pill had a pharmacological agent, which is good for his/her condition. This is the placebo effect⁽¹⁶⁾.

Many studies have reported the relevance and extension of this phenomenon. Most of them have focused on the effectiveness in subjective discomforts, such as pain, anxiety and depression; however, there are numerous investigations describing its physiological effects: heart functions effects, hyperlipidemia⁽¹⁷⁾, healing of wounds⁽¹⁸⁾ and even extended life of patients suffering cancer⁽¹⁹⁾, just to name a few of these studies.

THEORIES ABOUT ACTION MECHANISMS

Even though the placebo effect, probably has always existed in medicine⁽²⁰⁾, studies regarding its action mechanism have not devised an agreed explanation so far; instead of that, only various hypothesis are available, and each of them assume to be the right one⁽²¹⁾.

From a psychological point of view there are many mechanisms contributing to the placebo effect; these include expectations, conditioning, learning history, memory, motivation,

somatic aspects, reward, anxiety reduction, and senses⁽²²⁾. Even though there are more research regarding these placebo effect mechanisms, the conditioning hypothesis and the expectations hypothesis are two theories currently competing in the research area.

The first psychophysiological hypothesis uses the operant conditioning theory, where beneficial situations are learned and memorized; and then returned under the same conditions, except for one: the active product. With this theory we could explain the placebo effect and specially all the phenomenon known as placebo-sag, where accumulation of negative experiences with various therapies reduces the placebo effect⁽²³⁾. However, this hypothesis does not explain how the placebo effect may happen in the first situation, with no prior conditioning, or why we can see the phenomenon of familiarization in chronic diseases treatments, where with the same dosage, the effect decreases more and more and the placebo responds even worse as well, and their effect should be contrariwise. No doubt, we can see how this theory explains part of this mechanism, but it does not explain, the anticipatory trait and not only the reactive trait of the placebo response.

The second hypothesis is the theory of expectations. Currently it has become the most popular theory about this matter. It is based on the hypothetical expectation the patient has about the using a product would cause on him/her. Patient's expectations, hope and his/her eagerness to heal may arise the placebo effect. This theory is better understood as the cognitivist approach to the psychological explanation of the phenomenon. This theory provides a reflexive consciousness for generating expectations, therefore, the placebo effect would become an intentional and anticipatory act, consciously accessible, where the placebo effect may happen due to conditioning tests by means of a product, but also by means of other sources, such as verbal/social signs⁽¹⁶⁾. Even though this hypothesis has become prevailing in the psychological theory of the placebo effect, and it allows to deeply outline the physician's role in the patient's expectations, --which will be further reviewed--there are still some incomplete aspects in its drafting. The first element of discussion is the placebo effect, included

within bodily activities classified as skillful, and activities named as irreflexive. The skillful part is developed within a learning process. This is why psychologists build the Expectations Theory by means of cognitive processes involving cultural/social learning mediated/directed by conditioning tests. The problem is the difficulty to start a physiological response, by means of a conceptual or linguistic representation. In our daily life thinking about a specific part of our body or brain area is not enough for significantly alter its conduct. In this sense it is possible to argue that an agent, in this case the placebo, may have a representation of its action, but this functional representation works hidden. This is how the placebo response is suggested to use implicit/unconscious expectations⁽²⁴⁾. This leads us to the second component of the discussion. If expectations are not explicit constructs, its demonstration is subject to criticism and cannot be forged. If expectations measurements depend on the verbal self-report and expectations are defined as implicit, regardless of the result of an experiment, any researcher can challenge data reliability.

Even though the Theory of Expectations has limitations in terms of research, its foundation allows us to put the focus of the placebo effect, not on the placebo itself, but rather in the psychological/physiological response meaning, which is found in the origins or in the treatment of a disease⁽²⁵⁾.

PHYSICIANS AS HEALING AGENTS

Before color, shape or administration way, placebo effectiveness is first/mainly determined by the information provided by the physician. This is how medicine becomes significant for the patient, and the physician recognizes its valuation in his/her role as subject involved in a relationship with the patient.

The physicians' empathy capacity; their conviction in what they do; their confidence dedicated to their patients; their capacity to feel they can control the situation⁽²¹⁾; In short, the quality of the personal relationship he/she generates; all of them are quite crucial for the healing process, as these subjective aspects may, oftentimes and by themselves cause a physiological change expected from the medication or,

to a great extent, reinforce the *verum action*.

From the patient's point of view, the most important component for his/her improvement are the general qualities of the professional, whether he/she is a physician or a psychologist⁽²⁶⁾. Patients experiencing a cooperative/participative relationship is key for creating and keeping a partnership aimed to favor patients' improvement. Understanding this, both for the professional --who is willing to listen to as an active assistance component-- and for the physician --who provides the drugs for discomfort relief of the patient-- must be the foundation to believe it is possible to make a significant change in the life of others.

DISCUSSION

Currently, one of the most relevant health concerns is the need to limit expenses in this area. The most used method regarding this issue is to demand from treatments to prove their effectiveness. The approach that has most contributed to this need is evidence-based medicine.

From the 60s, for depression treatment, the standard implemented for approval of a psychotropic drug has been randomized clinical trial (RCT). RCTs have allowed to provide clinical orientation on the effect of medications and to limit existing variations in medical practice. However, this type of tests --used to learn about the specific effects of a treatment--

Have unexpectedly reasserted, the relevance and extension of this unexpected guest for biological psychiatry as placebo effects are.

As discussed at the beginning of this article, there is plenty of research that has proved a significantly poor/inexistent effectiveness regarding prevalence of the treatment with antidepressants and placebo-controlled groups. Just as stated by Khan et al.⁽²⁷⁾ in a systematic review, antidepressants are reported to work only slightly better than placebos. This low effectiveness is even weaker when studies are performed with a double blind, rather than when the researcher knows what is the control group. But even more relevant when questioning the role of antidepressants as the basis of depression treatment is the comparison with other treatments, such as psychotherapy or alternative treatments, where antidepressants report

the same effectiveness than other types of treatment and a slight increase, compared with the placebo effect.

These data reveal the need to perform a critical analysis of the prevalence of one treatment compared with the other, but even more, it highlights the need to deeply understand the action mechanisms underpinning interventions in mental health.

If we consider that the placebo effect appears in all type of interventions as the expectation the patient has to receive the benefits of a treatment or intervention, we must understand that placebos --which are inert substances--, has become a part of any potential healing process. In this sense, we think it is necessary to make a part of the current discussion regarding treatment for mental health pathologies, the various unspecific factors determining the success/failure of a treatment. Ignore these facts and insist on a biological psychiatry, not committing the patient in his/her relationship with the professionals, in the sense of his/her discomfort, in the development of an improvement expectation and in the importance of the therapeutical, means to quit demands for help to alternative approaches not considering, for instance, the need to reduce recurrence, people's direct expenses or its cost-effectiveness.

CONCLUSIONS

There are still many unexplored aspects in depression treatment and the implications to perform studies involving a placebo. Evidence-based medicine must not ignore elements hard to be quantified or explicit. Those so called unspecific factors may be very specific, such as the impact of the relationship or the impact on the patient regarding beliefs or expectations, and psychological mechanisms which from the base may be fruitful in all mental health interventions. Generation of scales aimed to better measure the placebo effect, and methods aimed to reduce thereof in this health area, could provide benefits for future clinical tests aimed to test the effect of psychiatric medication. The evidence we have gathered to date effectively proves that antidepressants have an active effect on patients, but in terms of public health, the effect could not be significant enough as to justify its

funding above other therapeutical alternatives.

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